**AMENDMENTS TO THE CLAIMS**:

This listing of claims will replace all prior versions, and listings, of claims in the application:

**Listing of Claims:**

Claims 1-19 (canceled)

Claim 20 (currently amended) A method of immunizing a ~~host against an annexin protein, annexin derived peptide or differentially modified annexin protein~~ patient having a cancer that is characterized by an increased expression of annexin protein in the patient, comprising ~~inoculating~~ administering to the ~~host with an~~ patient a purified annexin protein expressed by the cancer to which the patient has mounted an immune response admixed with an adjuvant, ~~antigen in a physiologically acceptable carrier,~~ wherein the immunization results in a production of antibodies directed against said annexin protein ~~antigen~~ and said antibodies inhibit tumor cell growth or facilitate killing of tumor cells.

Claim 21 (canceled)

Claim 22 (currently amended) The method of claim ~~21~~ 20 wherein the ~~disease is~~ cancer is a lung adenocarcinoma or a squamous cell carcinoma.

Claim 23 (canceled)

Claim 24 (previously presented) The method of claim 20 wherein the annexin protein is Annexin I.

Claim 25 (previously presented) The method of claim 20 wherein the annexin protein is Annexin II.

Claim 26 (previously presented) The method of claim 20 wherein the annexin protein is a modified protein.

## REMARKS

This amendment is in response to the Office Action mailed October 24, 2005 in the above-identified application. Applicants request a three-month extension of time and enclose the relevant fee.

Claims 1-26 are pending in this case, and have been subject to a restriction requirement. By this amendment, Applicants confirm the election of Claims 20-26 for prosecution in the present application. Applicants hereby cancel Claims 1-19 without prejudice and affirm the right to file the subject matter of Claims 1-19 in further divisional applications.

By this amendment, Applicants have amended Claims 20 and 22 and have canceled Claims 21 and 23. The support for these amendments may be found in the specification, e.g. pages 7 and 20 and in Claims 20-26 as filed in the Preliminary Amendment. No new matter has been added.

The Examiner has objected to the specification. In response, the specification has been amended to indicate that the present application is a divisional of Application Serial No. 09/370,337, now U.S. Patent No. 6,645,465. In addition, the specification has been amended to provide a further description of Figures 4-6 as requested.

Claims 20 and 24 have been rejected under 35 U.S.C. §102(b) as anticipated by Seemann et al. The Examiner alleges that Seemann et al. disclose immunizing a host with Annexin I to produce antibodies (in a rabbit). The antibodies were used to study Annexin I association with endosomes. Claims 20 has been amended to incorporate the subject matter of Claims 21 and 23, which were not rejected in view of Seemanns. In addition, the amendment to Claim 20 makes clear that the purified annexin protein which is administered to the patient is the one to which the

patient already produces antibodies as a result of its over expression by the patient's cancer. In view of the amendment, Applicants maintain that Seemanns neither teaches nor suggests Claims 20, as amended, and 24, dependent therefrom.

Likewise, Claims 20 and 25 have been rejected under 35 U.S.C. §102(b) as anticipated by Hullin et al. which allegedly discloses production of antibodies to Annexin II in a rabbit host. In view of the amendments to Claim 20, (and Claim 25, dependent therefrom) Applicants contend that Hullin et al. do not teach or disclose the presently claimed invention.

Claims 20 and 26 have been rejected under 35 U.S.C. §102(b) as anticipated by Sjolin et al. which allegedly teaches immunization of rabbits with a peptide containing an annexin consensus sequence coupled to KLH in order to produce antibodies. As provided above, Sjolin et al. do not teach or suggest Claim 20, as amended or Claim 26, dependent therefrom.

Claims 20-26 have been rejected under 35 U.S.C. §112 ¶1 as lacking an enabling disclosure of how to practice the claimed invention without undue experimentation. The Examiner argues that the claims are directed to immunotherapy of cancer and that the specification lacks sufficient guidance and objective evidence to teach one of skill in the art to predictably treat cancer by the claimed method.

Applicants respectfully disagree. The present specification specifically recites that the immunogen is an annexin I or II isoform to which the cancer patient mounts an immune response. The claims, as amended, are specifically directed to the particular purified annexin to which the patient produces antibodies. It would be reasonably understood that such annexin proteins are prepared from patient tumor derived cell lines that overexpress an annexin protein.

In a subsequent publication by the inventors, and their colleagues, carried out in accordance with the teachings of the present specification (Brichory et al., PNAS 98:9824-9829 (2001)), the common occurrence of annexin I and II autoantibodies and high levels of circulating IL-6 were again demonstrated in lung cancer patients. The authors showed that the immunogenicity of the proteins is correlated with N-linked glycosylation in the annexin antigens (at residue 42 in annexin I and residue 62 in annexin II, see page 9828, right hand column). Thus, there is a specific biochemical nature of the specific antigens.

Moreover, Brichory et al. demonstrate that the elevated levels of IL-6 in lung cancer patients plays a role in the increased expression of annexin proteins in cultured lung tumor cells and an increased transport of annexins into the cell membrane where they are exposed at the surface of the cells. According to Brichory et al. prior studies by Li et al., Cancer Immunol. Immunother. 47:32-38, 1998, had shown that annexin II derived peptides are presented on HLA II molecules in melanoma cell lines. In addition, Boehm et al., Am. Rev. Immunol. 15:749-795 (1997) showed that increased IL-6 in lung cancer produce an increase in MHC molecules. Taken together with the teachings of the specification, these studies show that the pre-requisites for an immune response against annexin proteins are present in lung cancer and that the presently claimed invention can be practiced without undue experimentation. Moreover, formulation and dosing regimens for immunogens are well known in the art and do not constitute undue experimentation.

The Examiner also argues that the nature of the claimed invention and the state of the art regarding cancer immunotherapy are highly unpredictable and cites to several papers by Bellone et al., Bodey et al. and Gaiger et al. for support for this proposition.

The art cited by the Examiner utilizes peptide vaccines (and not full length proteins as here), see, e.g. Bellone et al. In addition, unlike the present invention, the cited papers typically use peptides derived from proteins against which no innate humoral (antibody) response has been shown in patients with cancer, with the goal of eliciting a cellular immune response. Moreover, unlike the proteins of the present invention, the prior art immunizing peptides are generally synthesized and do not contain post-translational modifications, e.g. N-linked glycosylation, that are correlated with the immune response to annexins in lung cancer patients (Brichory et al.). In addition, the cited art, e.g. Bodey et al., does not dismiss the use of cancer vaccines out of hand, but provides specific utilities as "adjuvants to traditional therapies" and "management of residual disease" following surgery.

In addition, there are currently a number of specific subunit cancer vaccines in various stages of clinical developments which are proving quite effective (see e.g. attached report on the success of cervical cancer vaccines).

Applicants maintain that the art and the nature of the present invention are not as unpredictable as asserted by the Examiner. In the present case, the immunogen is characterized, and the patient already produces antibodies thereto. Thus, there is a reasonable likelihood that immunization with the particular annexin will lead to a beneficial immune response to the cancer in the patient.

Lastly, Claims 20-26 have been rejected under 35 U.S.C. §112 ¶1 as lacking an adequate written description of the claimed invention (new matter rejection). It is maintained that the amendments to Claim 20 overcome this specific rejection and that there is no new matter. Applicants requestly request withdrawal of the new matter rejection.